REMARKS

Claims 35-40 are pending in this application.

Applicants thank the Examiner for withdrawing the rejection of claims 27-41 under 35 U.S.C. § 101 for alleged lack of utility in the Office action mailed September 19, 2007. In that Office action, the Examiner acknowledges that the "MLR assay is an art accepted assay for identifying immune suppressive molecules and the assay is generally predictive of their *in vivo* effectiveness." Page 2 of the Office action mailed 9/19/07.

Claim Rejections

Rejection under 35 U.S.C. § 112, first paragraph:

Enablement

The only ground remaining for the rejection of claims 27-41 is under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. Specifically, according to the Office action, "[t]he assertion that the claimed invention could be useful for the treatment of conditions where the enhancement of the immune response would be beneficial is not enabled by the disclosure of the instant specification. The only use contemplated for the claimed invention is a therapeutic suppression of the immune system." Page 3 of the Office action mailed 9/19/07. In support, the Office action relies on Kahan, Picotti, and Campo and cites Kahan for the proposition that "no *in-vitro* immune assay predicts or correlates with *in-vivo* immunosuppressive efficacy; there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from *in vitro* systems to *in vivo* conditions." Pages 3-4 of the Office action mailed 9/19/07.

Applicants respectfully disagree. US Patent Nos. 7,220,835 and 7,282,570 are assigned to Genentech and share specifications similar to the specification at issue. Each of these patents contains claims that rely on an example disclosing results in an MLR assay to demonstrate utility and enablement. While Applicants acknowledge that each application is examined on its own merit, Applicants also point out that the Court of Customs and Patent Appeals recognized that **"similar claims allowed by the Patent**

Office tribunals furnish evidence of what features those tribunals regard as patentable." *In re Schecter and LaForge,* 205 F.2d 185, 98 USPQ 144, 150 (CCPA 1953). Thus, issuance of the claims in US Patent Nos. 7,220,835 and 7,282,570 based on substantially similar applications, supported by substantially identical disclosures of results obtained from the MLR assay is persuasive evidence that should be considered in determining whether the presently claimed invention satisfies the enablement requirement.

Further, as explained at Section 601 of the MPEP, it is well established that information which is well known in the art does not have to be described in detail in the specification:

> Where elements or groups of elements, compounds, and processes, which are conventional and generally widely known in the field to which the invention pertains, form a part of the invention described and their exact nature or type is not necessary for an understanding and use of the invention by a person skill in the art, they should not be described in detail.

At the time the present application was filed, one of ordinary skill would have clearly been able to identify conditions where the suppression of immune response is beneficial. For example, at the effective filing date of this application it was known that transplant patients suffering from host versus graft disease would benefit from the suppression of their immune response. *See* Fung-Leung *et al. Transplantation,* 60:362-8 (1995), (previously submitted), U.S. Patent No. 5,817,306, filed June 7, 1995, and U.S. Patent No. 5,648,376, filed January 19, 1995. As shown these references, inhibitors of T-cell proliferation, such as PRO361, can be used in the treatment of undesirable immune responses such as graft versus host disease.

Additionally, each of Kahan, Picotti, and Campo, relied on by the Office action, study allograft rejections and immunosuppression of graft rejection using test compounds studies *in vitro.* Kahan is inconsistent with what was known and accepted in the art at the time of filing regarding the MLR assay. For example, U.S. Patent No. 5,817,306 states, "The mixed lymphocyte response (MLR) and phytohemagglutinin A (PHA) assays are valuable for identifying immune suppressive molecules in vitro that are useful for treating

graft versus host disease. The results obtained from these assays are generally predictive of their in vivo effectiveness" (Column 12, lines 36-41; emphasis added). U.S. Patent No. 5,801,193, filed April 15, 1997, states that "[t]he MLR is an assay recognized by those skilled in the art as an in vitro predictor of in vivo immunosuppressant activity." (Column 8, lines 8-10, emphasis added). U.S. Patent No. 5,648,376, filed January 19, 1995, states that "[a] measure of immunosuppressive activity that serves as a model for transplantation rejection is inhibition of cell proliferation in a mixed lymphocyte reaction (MLR) assay." (Column 11, lines 24-26).

The Office action cites Picotti et al. as demonstrating that "IL-12 enhances alloantigen specific immune function as determined by MLC, but this result in vitro does not result in a measurable response in vivo (i.e. failure to accelerate allograft rejection)." Pages 3–4 of the Office action mailed 9-19-07. Applicants first note that the asserted utility of PRO361 is not accelerated allograft rejection, which is hardly a process that medical practitioners would wish to accelerate. Thus, the fact that IL-12 does not accelerate allograft rejection is not relevant to the enablement for PRO361, which has the opposite effect from IL-12 in that it suppresses the immune response. It is already well established in the art that molecules which inhibit the MLR response are useful in the suppression of immune reactions in vivo, as demonstrated for example by U.S. Patent Nos. 5,817,306, 5,801,193, and 5,648,376, and 5,958,403, as discussed above. Nor is the failure of IL-12 to accelerate allograft rejection an indication that IL-12 does not possess general immunomodulatory properties in vivo. Picotti et al. confirm that "1L-12 is also a key cytokine involved in promoting cell mediated immune responses in vivo" (page 1459, col. 1).

The Office action further asserts that Campo et al. "demonstrate that while zinc suppresses alloreactivity in MLC, it does not decrease T-cell proliferation in vitro nor produce immunosuppressive effects in vivo." Page 4 of the Office action mailed 9-19-07. Applicants respectfully point out that the Office action has misinterpreted this statement, due to the fact that the authors refer to two different types of immunosuppressive effects. Campo et al. set out to look for an inhibitor of MHC in vitro which would have the fewest

side effects in vivo (see Abstract). The authors note that high concentrations of zinc "impair all T cell and monocyte function" (page 20; emphasis added). The authors took this impairment as an indicator of toxicity, and therefore intentionally used concentrations of zinc below that at which all T-cell function was impaired, in order to identify a concentration range that would not result in toxic effects. However, that does not mean that Campo et al. found zinc to have no immunosuppressive activity in vivo. In fact, the authors conclude, based upon their MLC results, that "zinc could become an immunosuppressant in transplantation medicine without toxic side effects" (page21; emphasis added). Thus Campo et al. supports Applicants' position that those of skill in the art would interpret the results of MLC assays as having physiological relevance.

Additionally, Applicants note that the Office action has failed to point out several instances within these cited references wherein the authors stated that the MLR is an important method with a good predictive value. For example, Campo et al. teach that "the human mixed lymphocyte culture (MLC) is an important method to test donor-recipient compatibility in bone marrow transplantation. It could be shown that cytokine release, especially IFN-, has a very good predictive value with regard to the transplantation outcome, as cytokines play a major role in the generation of an alloreactive immune response and for the induction of graft rejection in vivo..... Landolfo et al. inhibited T-cell reactivity by the addition of anti-IFN-both in vitro and in vivo" (see page 18; emphasis added). Further, Picotti et al. showed that the IL-12RS1 subunit was critical for IL-12 driven enhanced alloimmune response in vitro and in vivo (see abstract). Thus, while there are instances of unpredictability using the MLR assay, there are many studies showing predictable results, including studies from Picotti, Landolfo and the IFN- study. Finally, Campo et al. teaches that "cyclosporin A, FK506, and other substances are used to prevent graft rejection. In vitro experiments revealed an inhibition of the MLC" (page 16). Thus the teachings of Campo et al. confirm that inhibition of the MLR is observed for known immunoinhibitory molecules that are in actual clinical use.

In summary, Applicants respectfully submit that the Office action has not shown that a lack of correlation between results of the MLR assay in vitro and immunomodulatory activity in

vivo is typical. In fact, Picotti et al. and Campo et al. support Applicants' position that the in vitro MLR assay can be successfully used to identify compounds having immunomodulatory activity, particularly immunoinhibitory activity, in vivo. Applicants' position is further supported by additional references in the art which demonstrate that inhibitors of the MLR find utility in suppressing unwanted immune response, and thus suppress unwanted graft rejection. For example, the ability of tepoxalin, an immunomodulatory compound, to suppress graft-versus-host reaction, has been demonstrated using the MLR assay (Fung-Leung et al., Transplantation 60:362-8 (1995); made of record in Applicants' filing of 9/2/2005).

The Office action continues that "[t]he results of the MLR assay in the instant specification are merely preliminary, and much more experimentation is necessary for one of ordinary skill in the art to use the claimed invention in the manner disclosed." Page 4 of the Office action mailed 9-19-07. "This experimentation would be undue, because until it is performed, the skilled artisan cannot use the claimed invention in the manner disclosed." Page 4–5 of the Office action mailed 9-19-07. Applicants respectfully disagree.

Applicants respectfully submit that enablement "is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive." As the M.P.E.P. states, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." The M.P.E.P. further explains that "If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. § 112 is satisfied" Applicants note that the specification clearly indicates that the claimed polypeptides are useful in the treatment of undesirable immune responses such as graft versus host disease. The use of immunosuppressive molecules in the treatment of such disorders is well known in the art, as indicated by Kahan et al., Picotti et al. and Campo et al., made of record by the Office action, as well as Fung-Leung et al., Shim et al., and U.S. Patent Nos. 5,817,306, 5,648,376, 5,801,193, and 5,958,403 (all made of record in Applicants' filings of 9/2/2005 and 3/6/2006). Thus, any further experimentation required

to determine, for example, the particular dosage or method of administration of PRO361 would not be considered undue. Indeed, there is no requirement to determine exact dosages in order to demonstrate efficacy.

Moreover, as discussed above, it is well established in the art that a positive result as an inhibitor in the in vitro MLR assay is reasonably correlated to use as a therapeutic compound for the treatment of conditions such as graft vs. host disease. See, for example, Fung-Leung et al., and U.S. Patent No. 5,817,306, filed June 7, 1995, U.S. Patent No. 5,648,376, filed January 19, 1995, and U.S. Patent No. 5,958,403, filed July 11, 1994 (all made of record in Applicants' filings of 9/2/2005 and 3/6/2006). The Office action has acknowledged as much by stating that "the MLR assay is an art accepted assay for identifying immune suppressive molecules and the **assay is generally predictive of their in-vivo effectiveness**." Page 2 of the Office Action mailed 9-19-07; emphasis added. Thus, by providing Example 34, which demonstrates that PRO361 tested positive as an inhibitor in the MLR assay, the instant specification has provided all that is required to demonstrate enablement for the claimed PRO361 polypeptides.

Applicants strongly disagree with the Office action's reliance on the reported fact that TGN1412, aimed at treating leukemia and autoimmune diseases, when administered to volunteers, caused serious side-effects leading to hospitalization. Such facts are entirely irrelevant to the assessment of patentability, and in particular to the issue of enablement. Investigation of issues like safety and tolerability of a drug should be left to the judgment of the FDA, the federal agency having the mandate to issue market authorizations.

In conclusion, the use of the MLR assay is well established for the identification of immunomodulatory compounds, including compounds that inhibit and compounds that stimulate the immune response. Accordingly, based upon the disclosure of the present application and the general knowledge in the art that was available at the time the present invention was made, one of ordinary skill in the art would have been able to use the claimed polypeptides for the intended purpose (immune suppression) without undue

experimentation. Therefore, Applicants respectfully request that the enablement rejection of Claims 35-40 under 35 U.S.C. § 112, first paragraph, be withdrawn.

CONCLUSION

Applicants believe this Request for Reconsideration fully responds to the Office action mailed September 19, 2007. Applicants respectfully request the Examiner grant allowance of pending claims 35-40. The Examiner is invited to contact the undersigned attorney for the Applicant via telephone if such communication would expedite allowance of this application.

Respectfully submitted,

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